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10/019,495	10/23/2001	Jennifer L Hillman	PF-0698 USN	4335
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FOLEY AND LARDNER SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			EXAMINER BASI, NIRMAL SINGH	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/019,495

Applicant(s)

HILLMAN ET AL.

Examiner

Nirmal S. Basi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 29 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-15,17,18,20,21 and 23 is/are pending in the application.
- 4a) Of the above claim(s) 7,9,12-14,17,18,20,21 and 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8,10,11 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicants' election with traverse of Group I A (Claims 1-6, 8, 10-11 and 15), pertaining to the protein of SEQ ID NO:9, encoded by the nucleic acid of SEQ ID NO:26, on 7/29/04, is acknowledged. The traversal is on the ground(s) that " the Commissioner has decided to permit a reasonable number of such nucleotide sequences to be claimed in a single application" so as to further aid the biotechnology industry in protecting its intellectual property." Further the applicants argues, "the Patent Office has determined that normally ten sequences constitute a reasonable number for examination purposes" and that that number does not create an undue burden on the Office". For this reason, Applicants contend that the polynucleotides depicted in SEQ ID NO:22-25, corresponding to Groups B-V to B-VII1, and SEQ ID NO:27-31, corresponding to Groups B-X to B-XIV, should be examined alongside the polynucleotides of SEQ ID NO:26. Accordingly, Applicants request that the Examiner rejoin SEQ ID NO:22-25 and SEQ ID NO:27-31 and examine together the polynucleotides of Groups B-V to B-XIV. Applicants' arguments have been fully considered but are not found persuasive. A search of requested groups and sequences would not be co-extensive particularly with regard to the literature search. The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. The special technical feature of the claimed group is the protein of SEQ ID NO:9, encoded by the polynucleotide of SEQ ID NO:26.

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None of the other sequences share this special technical feature, as each defines a separate contribution over the art. Further there is no requirement that the Office examine more than one sequence. In instant case an examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Further Applicant is required to cancel/amend elected claims pertaining to non-elected invention, i.e. relating to the polynucleotides of SEQ ID NOs: 1-8, 10-17 and their encoded polypeptides.

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejection, 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-6, 8, 10-11 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 is indefinite because it is not clear when a polynucleotide (nucleic acid) is considered naturally occurring as compared to when it is not naturally occurring so as to allow the metes and bounds of the claim to be determined. If one makes a

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nucleic acid molecule having at least 90% sequence identity to SEQ ID NO:26 in the laboratory by randomly mutating, say one base, of the nucleic acid molecule disclosed in SEQ ID NO:26, would said mutated nucleic acid molecule be considered "naturally occurring" or not "naturally occurring". At this moment in time this determination is impossible to make. Not until every possible sequence and mutation in every living cell has been determined, to serve as a comparison, can one even begin to formulate an opinion as to whether the nucleic acid molecule is "naturally occurring". If the mutation created in the laboratory, which was initially classified as not naturally occurring, is found in a living cell, does the nucleic acid molecule then become naturally occurring? Therefore by merely looking at a nucleic acid molecule it cannot be determined if a sequence is naturally nucleic acid molecule as compared to not naturally occurring. What specific critical feature of the invention allows the nucleic acid molecule to be classified as naturally occurring as compared to not naturally occurring? Further any recombinant nucleic acid introduced into a host cell and that replicates in said host cell could be considered naturally occurring.

Claims 1 is indefinite because it is not clear when a polypeptide molecule is considered naturally occurring as compared to when it is are not naturally occurring so as to allow the metes and bounds of the claim to be determined. If one makes a polypeptide having at least 90% sequence identity to SEQ ID NO:9 in the laboratory by randomly mutating, say one amino acid, of the polypeptide disclosed in SEQ ID NO:9, would said polypeptide molecule be considered "naturally occurring" or not "naturally occurring". At this moment in time this determination is impossible to make. Not until

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every possible sequence and mutation in every living cell has been determined, to serve as a comparison, can one even begin to formulate an opinion as to wheatear the polypeptide is "naturally occurring". If the mutation created in the laboratory, which was initially classified as not naturally occurring, is found in a living cell, does the polypeptide molecule then become naturally occurring? Therefore by merely looking at a polypeptide molecule it cannot be determined if a sequence is naturally nucleic acid molecule as compared to not naturally occurring. What specific critical feature of the invention allows the polypeptide to be classified as naturally occurring as compared to not naturally occurring? Further could any polypeptide produced by a recombinant nucleic acid introduced into a host cell be considered naturally occurring?

Claims 1 is indefinite because it is not clear what biological activity is contained in the fragment so as to allow the metes and bounds of the claim to be determined. If one makes a nucleic acid molecule

Claims 2-6, 8, 11 and 15 are rejected for depending upon an indefinite base (or intermediate) claim.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

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terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 10-11 and 15 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A "specific utility" is a utility that is specific to the subject matter claimed, as opposed to a "general utility" that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known or immediately apparent, which can be implied by the specification alone, or taken in combination with the knowledge of one skilled in the art. A "well established utility" must also be specific and substantial as well as credible. Based on the record, there is not a "well established utility" for the claimed invention. The specification has asserted utilities for the specifically claimed invention of claims 1-6, 8, 10-11 and 15.

The claims are directed to isolated nucleic acid encoding of SEQ ID NO:26 encoding the polypeptide of SEQ ID NO:9, variants and fragments of said polynucleotide and nucleic acid, vector and cell containing said nucleic acid and protein, and method of producing said protein. :

This specification (page 1) discloses the invention relates to nucleic acid and amino acid sequences of human membrane-associated proteins and to the use of these

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sequences in the diagnosis, treatment, and prevention of cell signaling, cell differentiation, and cell proliferation disorders. The specification discloses hundreds of disorders that may be associated with claimed invention. The claimed nucleic acid and protein are found in both normal and diseases tissue (Tables). The claimed polypeptide is disclosed to have some sequence homology to human sperm specific surface protein (Tables). The percent homology is not disclosed. There is no disclosure within the instant specification on what specific function the claimed protein possesses, or how to specifically assay for such; nor are any disease states disclosed that are directly related to claimed protein or nucleic acid dysfunction.

Accordingly, the instant specification provides insufficient guidance on "how to use" the disclosed proteins and therefore the nucleic acids of the instant invention, because no function for the claimed protein is known, or disclosed. Likewise, expression vectors and host cells whose sole function is to make claimed proteins lack utility for these same reasons. In order to practice the invention one of skill in the art would have to identify proteins and nucleic acids encoding claimed proteins having unknown activity. However, the specification does not provide a disclosure for identifying said activity. In particular, no assays are described in the specification by which one of ordinary skill in the art could extrapolate as to what constitutes functional characteristics of the claimed polypeptide, except for having the polypeptide sequence of SEQ ID NO:9 which is encoded by the polynucleotide of SEQ ID NO:26. Therefore, because it is unknown, nor disclosed, what specific ligand/agonist/ antagonist interacts or binds to claimed invention, it would be impossible for the skilled artisan to determine

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how to use Applicants' invention, as claimed without requiring undue experimentation to first discover the function/activity of claimed polypeptide as well as what unique ligands that interact with said polypeptide. Further, the specification does not teach which particular amino acids are critical for function of the polypeptide encoded by the polynucleotide of SEQ ID NO:26. Structurally deficient polynucleotides containing random mutations would be expected by the skilled artisan to result in nucleic acid molecules encoding inactive proteins, even if such activity becomes known. Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for claimed polypeptide function, if ever discovered, would prevent the skilled artisan from determining whether any modification or mutation to the claimed polypeptide/polynucleotide could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within polypeptide itself would be predicted to adversely alter its biologically active 3-dimensional conformation, without undue experimentation to determine otherwise; especially when no assays to distinguish such functional polypeptide/polynucleotide are known or disclosed.

The utilities asserted by Applicant are not specific or substantial. No specific function of the polypeptide of instant invention is known. Neither the specification nor the art of record disclose the polypeptide of SEQ ID NO:9, or fragments thereof, useful to identify drugs that affect said protein and modulate its activity. Neither the specification nor the art of record disclose the nucleic acid of SEQ ID NO:26, or

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fragments thereof, useful to identify drugs that affect the protein encoded by said nucleic acid molecule and modulate its activity.

Similarly, neither the specification nor the art of record disclose any instances where disorders can be affected by interfering with the activity using the polypeptide of SEQ ID NO:9 or fragments thereof. Thus the corresponding asserted utilities are essentially methods of using polypeptide of SEQ ID NO:9/nucleic acid of SEQ ID NO:26 or fragments thereof to identify disease states associated with claimed polypeptide dysfunction and as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with claimed polypeptide which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed polypeptide or nucleic acid and fragments thereof, further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See *Brenner v. Manson*, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Neither the specification nor the prior art discloses polymorphism (allelic variants) of instant invention. Further, the specification, nor prior art suggests any disease states where the protein of instant invention is involved. Tissue identification is a general utility applicable to all nucleic acids. All members of a family of proteins may be used for tissue identification and screening of candidate drugs. However, for a utility to be "well-established" it must be specific, substantial. However, the particulars of screening of candidate drugs, that target claimed polypeptide and in toxicology testing are not disclosed in the specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:9 and 26 and fragments thereof. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed invention is only useful in the sense that the information that is gained from the assay is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the family. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants' individual polypeptide is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation

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for the result, and none is known in the art. Given this consideration, the claimed method of using the polypeptide of SEQ ID NO:9 or nucleic acid of SEQ ID NO:26 have no "well-established" use. The artisan is required to perform further experimentation on the claimed invention itself in order to determine to what "use" any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the claimed invention and a disease or disorder. The presence of claimed polypeptide/polynucleotide in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed invention and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed invention to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of claimed invention as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed invention and any disease or disorder and the lack of any correlation between the claimed polypeptide/polynucleotide with any known disease or

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disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Without knowing a biological significance of the claimed polypeptide/polynucleotide, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible "real world" manner based on the diversity of biological activities of claimed polypeptide/polynucleotide. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, does not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide encoded by the claimed nucleic acid. One of ordinary skill in the art must understand how to achieve an

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immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:9 and the polynucleotide of SEQ ID NO:26. The specification has not described the claimed polypeptide/polynucleotide in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:9 or the polynucleotide of SEQ ID NO:26, variants and fragments thereof have any substantial use. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for the diagnosis, treatment, and prevention of cell signaling, cell differentiation, and cell proliferation disorders are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed polypeptide/polynucleotide might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria. See *In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the

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intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The rejection under § 101 follows *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. See, e.g., *In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed nucleic acid/polypeptide, vectors containing said nucleic acid, cells containing said nucleic acid or said vector has no utility, methods of its use are also rejected for lack of utility.

5. Claims 1-6, 8, 10-11 and 15 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above,

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one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the polypeptide of SEQ ID NO:9 encoded by the polynucleotide of SEQ ID NO:26, variants thereof, vectors containing said nucleic acid, cells containing said nucleic acid or said vector, methods of its use, further experimentation is necessary to attribute a utility to the claimed invention.

Further, the claims are drawn to a nucleic acid encoding a polypeptide with no disclosed function. The claimed nucleic acid encodes an orphan polypeptide whose activity, activating ligands and functionality have not been disclosed. Therefore nucleic acids encoding unrelated and inactive proteins are encompassed by the claims. The specification does not disclose how to produce active variants or how to use inactive ones. Substitutions that result in active variants are not disclosed. Substitutions that are detrimental to claimed invention functionality are not disclosed. Therefore the production of active variants with 90% identity to claimed invention are not disclosed. The claim encompasses billions and billions of variants but no disclosure of how to assay active variants. The ligand and function of the claimed invention is unknown.

The complex nature of the invention and the unpredictability of assigning a function to claimed polypeptide with no known ligand, activity, or function is described in the rejection under 35 USC § 101 and 35 USC § 112, 1st paragraph, above.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above,

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one skilled in the art would not know how to use and make the claimed invention so that it would operate as intended without undue experimentation.

Further, claim 15 is rejected based on the failure of the specification to enable one of skill in the art to make and/or use the pharmaceutical composition encompassed by the claim. The pharmaceutical composition comprising the polypeptide of claim 1, or fragments thereof, infers a drug or medication with therapeutic activity. The specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claim without undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (8 USPQ2d 1400 (CA FC 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented. The term "pharmaceutical" implies a treatment of a disease. It is unpredictable what diseases could be effectively treated using a "pharmaceutical composition" comprising a the composition of claim 15. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be treated by administering a "pharmaceutical composition" comprising the protein of claim 15. Attempting to identify a disease treatable by such a "pharmaceutical composition" would constitute undue experimentation. Therefore one of skill in art would have to identify a disease treatable by said "pharmaceutical composition", determine effective compositions, determine effective doses to achieve the intended purpose, determine routes of effective

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administration, determine if the "pharmaceutical composition" can reach its target tissue without degradation and determine if it has a therapeutic effect, all of which would constitute undue experimentation. Therefore, the unpredictability to achieve all the afore mentioned goals and the lack of guidance provided in the specification, the disclosure fails to enable one of skill in the art how to make and/or use the "pharmaceutical composition" encompassed by the claim 19.

6. Claims 1-6, 8, 10-11 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to polynucleotides and polypeptide having at least 90% sequence identity with SEQ ID NO:26 and SEQ ID NO:9, respectively. The claims are further directed to isolated nucleic acid encoding comprising fragments of SEQ ID NO:26, immunogenic fragments of the polypeptide of SEQ ID NO:9, biological active fragments, vector and cell containing said nucleic acid and protein, and method of producing said protein. :

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

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chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid/polypeptide, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's/polypeptides that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed nucleic acid/polypeptide sequences, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. The claims are not even directed to polynucleotides which encode a particular functional protein. The biological activity of the polypeptide is not disclosed. Therefore nucleic acids encoding non-functional or functionally unrelated

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proteins are encompassed by the claims. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specific activity of the protein of SEQ ID NO:9. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

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To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}). The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \dots + X^{n-1}L(L-1)(L-2)\dots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\dots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23} . Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26} . So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by

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the formula $X^n L^n / n!$, where $n \ll L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26} . For a 300-nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56} .

In the present case, the reference amino acid sequence, SEQ ID NO:9, is 651 amino acids long, and the reference nucleotide sequence, SEQ ID NO:409 is 3694 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 90% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6×10^{23} and 1.6×10^{56} , respectively. While limiting the scope of potential sequences to those that are at least e.g. 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen*, *Fiers*, and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active claimed polypeptide that would improve

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or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology and identical biological activity with SEQ ID NO:9, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active polypeptide with an amino acid sequence differing from SEQ ID NO:9 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:9, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:9 encoded by SEQ ID NO:26 which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

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encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:9 but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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7. Claims 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs et al (US Patent Number 5,976,838). Claims 1 is drawn to an isolated polypeptide comprising an immunogenic fragment of the polypeptide of SEQ ID NO:9.

Jacobs discloses a polypeptide (SEQ ID NO:21), which based on the sequence comparison provided, has 41.9% query match and 57.9% best local similarity to the polypeptide of SEQ ID NO:9. The polypeptide of Jacobs contains numerous immunogenic fragments contained in the polypeptide of SEQ ID NO: 9, e.g., amino acids 436-464, absent evidence to the contrary.

Therefore, Jacobs meets the limitations of claims 1, absent evidence to the contrary.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
October 18, 2004

NSB

Michael D. Pak
MICHAEL PAK
PRIMARY EXAMINER